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Review

Chitosan-based structures for skin repair: A literature review

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ABSTRACT

The use of chitosan in technological and biomedical applications has gained significant relevance due to its functional properties. Among its biological activities, its hemostatic, analgesic, antibacterial and anti-inflammatory activities make this natural biopolymer one of the most promising in the development of structures for skin repair. Its application and effects can be optimized by exploring efficient structuring techniques. In this context, this review is based on scientific evidence reported in the last decade regarding the development and use of chitosan-based structures in the skin repair process to show the most common structuring methods, the main mechanisms of action of chitosan, and its potential applications in skin repair processes. Additionally, this article brings a compilation of scientific and commercial works on the use of chitosan-based structures, in addition to vitro and/or in vivo results.

1. Introduction

The promising use of biomaterials for total or partial replacement of tissues or organs has significantly increased the amount of scientific research dedicated to approaches based on the development and use of new materials in the treatment of damage to skin tissues. In this scenario, the polysaccharides chitin and chitosan (CS) and even their derivatives have been widely applied, being considered suitable materials for natural tissue repair [1–3].

CS is a natural polycationic biopolymer found in cell walls and spores of some species of fungi [4]. However, it is mainly obtained from chitin deacetylation reaction. Chitin, a linear-chain polysaccharide, is mostly formed by 2-acetamido-2-deoxy-D-glucopyranose (GlcNAc) units linked by $\beta(1 \rightarrow 4)$ glycosidic bonds, while 2-amino-2-deoxy-D-glucopyranose (GlcN) units linked by the same type of bond predominate in CS chains [5,6]. The differentiation between these two polysaccharides is the percentage of GlcNAc and GlcN units: if the percentage of GlcN groups is greater than or equal to 50 %, the polymer is called CS. The chemical structure of CS provides superior physicochemical properties compared to chitin, primarily due to its ability to dissolve in acidic conditions. This solubility results from the presence of amino groups, which impart to CS a pH-responsive behavior. Such responsiveness makes chitosan highly desirable for various applications in the food, beverage, agrochemical, cosmetic, and pharmaceutical industries among others [7]. In the biomedical field, these physicochemical properties enable its application in various areas, evidencing its action as an antimicrobial agent and its use in controlled drug delivery, transfection, cholesterol and body weight reduction, and tissue engineering [8,9]. Specifically in tissue engineering, it can be employed in the development of structures that favor the tissue repair process, including skin repair [10].

The biomedical potential of CS arose in the mid-20th century, driven by advances in polymer science. Early applications, which were first documented between the 1960s and 1980s, were centered on wound healing, hemostasis, and surgical sutures [11]. After the discovery and establishment of nanotechnology in the 1900s–2000s, such applications were extended to the development of drug delivery systems and the tissue engineering area, introducing hydrogels and sponges formed by CS [12,13]. After the 2010s, modern innovations focused on the development of composites and smart biomaterials for wound care, antimicrobial coatings, and regenerative medicine emerged [14]. Nowadays,

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research on CS continues to focus on personalized medicine and smart biomaterials for healthcare and therapeutic solutions [1].

CS stands out as the only naturally occurring cationic biopolymer, giving it unique properties compared to other biopolymers. Derived from chitin and abundant in shellfish, it is a low-cost and sustainable option, unlike collagen, which often relies on more expensive and less sustainable animal sources. Its high biocompatibility reduces the risk of adverse reactions, different from animal-derived collagen, such as bovine or porcine, which may pose immunogenic risks. One of the key advantages of CS is its intrinsic antimicrobial activity against a wide range of bacteria, fungi, and viruses – an activity that collagen and hyaluronic acid do not significantly possess. Additionally, CS promotes rapid blood clotting, making it highly effective in controlling bleeding, whereas biopolymers like alginate and gelatin absorb exudate, but with limited hemostatic action. CS also forms a breathable, semi-permeable film that maintains optimal moisture levels, supporting accelerated wound healing. This ability to create a physical barrier is not found in hyaluronic acid, which despite retaining moisture, does not offer the same structural protection.

In this sense, the anti-inflammatory, antifungal, antioxidant, blood compatible and antimicrobial biological properties of CS, combined with its interesting characteristics of biocompatibility, biodegradability and non-toxicity, have made it a potential candidate for skin wound healing and repair [15]. Another important feature of CS is its versatility of processability, which allows the use of a wide number of structuring techniques for the production of nanoparticles (NPs), electrospun nanofibers (NFs), hydrogels, nanoemulsions, thin films, freeze-dried materials and sponges among others. Although these appealing properties and characteristics encourage researchers to develop CS-based materials for wound healing treatment, there are still some issues to be considered.

Some limitations include the poor solubility, poor mechanical properties and limited ability of chitosan to absorb exudates. These points have been overcome through the incorporation of drugs, metallic NPs, other polymers, or even other materials, forming CS-based hybrid structures [16] that promote more solubility, improve mechanical properties and increase exudate absorption. Finally, an additional challenge is the different physicochemical characteristics found in CS samples (depending on the medium used) and the difficulty in standardizing them (since they depend on the source). Many biological properties of chitosan are influenced by its structural characteristics (i.e., molecular weight and degree of acetylation), for example, its activity against microorganisms [17]. All these limitations make it difficult to consolidate the use of CS-based materials in clinical practice for wound treatment. For this reason, many researchers have sought to find ways to overcome such challenges.

In this context, this work presents a detailed overview of the literature containing recent advances on the use of CS for repairing skin lesions, with a special focus on its promising biological properties and the technology used for processing. Furthermore, we discuss the different CS-based architectures that can be obtained, with an emphasis on their application in tissue engineering. Fig. 1 summarizes the main topics covered in this review.

2. Biological properties of chitosan in the skin repair process

Skin wounds resulting from surgeries, burns, abrasions, and other traumas are common conditions encountered in clinical practice and are often associated with pain, functional disability, and even death [18]. For tissue repair to occur satisfactorily, the sequential processes of hemostasis, inflammation, proliferation, and maturation/remodeling are essential [19]. In this sense, CS has been widely studied for application in wound dressings due to its important role in all stages of skin wound repair [10,20].

The initial phase of repair, that is, hemostasis, is characterized by the immediate activation of the coagulation system, which follows vasoconstriction and platelet aggregation. During this stage, fibrinogen is converted into insoluble fibrin by enzymes, leading to the formation of

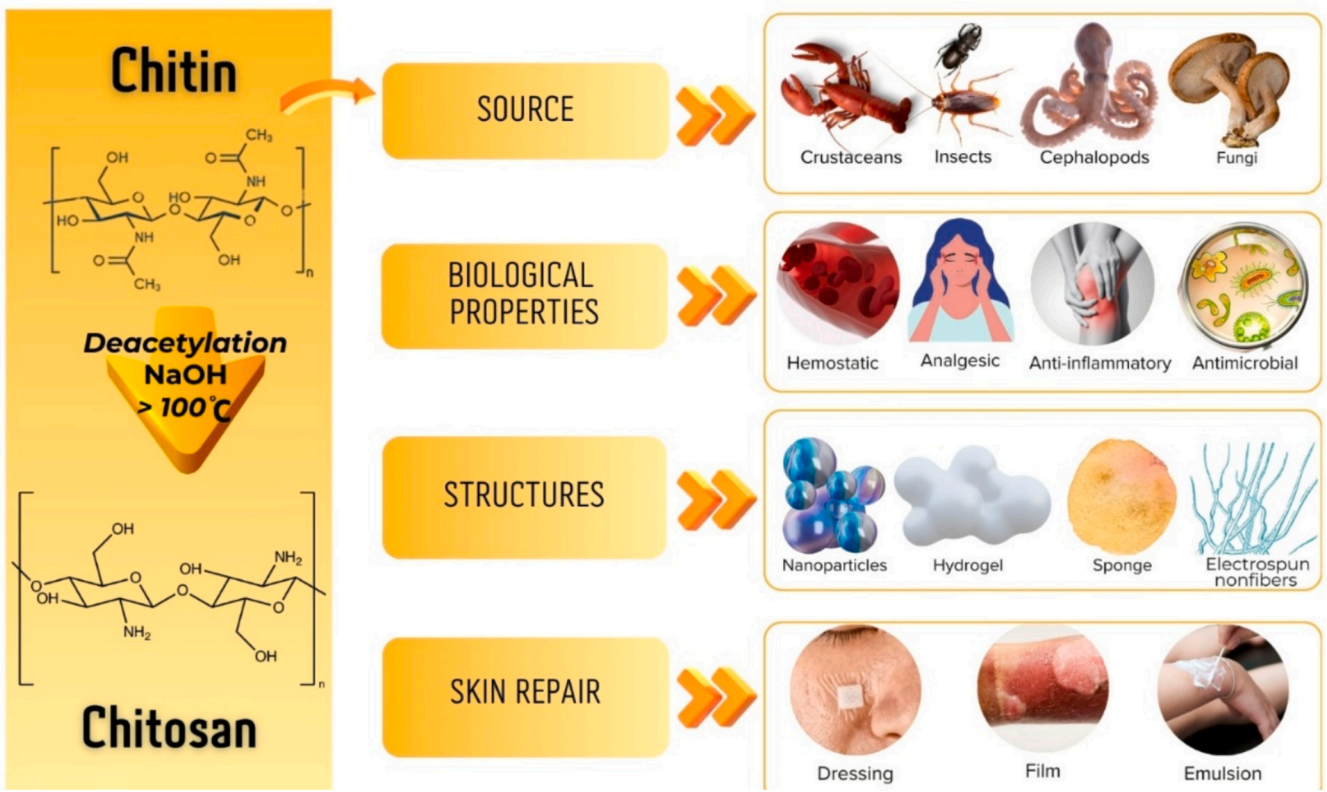

Fig. 1. Schematic representation of sources, biological properties, different types of structures and applications of CS in skin repair.

blood clots and ensuring local hemostasis. Current literature has shown that CS assists in the hemostasis process during the initial stages of repair, promoting platelet adhesion and aggregation, inducing erythrocyte (type of blood cell) aggregation, and inhibiting fibrinolysis (degradation of a blood clot fibrin network) [10]. Additionally, CS is known to increase the expression of glycoprotein IIb/IIIa in platelet membranes, thereby stimulating platelet adhesion to the vascular wall and platelet aggregation [21]. Another study reported that the positive charges of CS result in platelet aggregation resulting from the interaction with a large amount of negatively charged substances on the surface of activated platelets [22]. This interaction has a fundamental pharmacological action in hemostasis.

In the inflammatory phase of repair, mast cells (a type of connective cell) release histamine, leading to vasodilation and the recruitment of inflammatory cells, including neutrophils (type of white blood cell) and macrophages, to the injury site. In addition to playing a crucial role in phagocytizing pathogens and dead cells, these cells also release cytokines (signaling proteins that mediate cellular functions) and growth factors (subset of cytokines) that aid in molecular and cellular repair processes [19,23]. Indeed, anti-inflammatory effects of CS are mediated through several interconnected mechanisms. CS plays a role in modulating the inflammatory response by decreasing the production of pro-inflammatory cytokines, such as interleukin-1β, interleukin-6, and tumor necrosis factor-alpha (TNF-α). It also helps alleviate oxidative stress by reducing the generation of ROS (reactive oxygen species) [20,24]. Moreover, CS can regulate the secretion of inflammatory mediators and enhance the activation of immune cells, including macrophages, neutrophils, and polymorphonuclear leukocytes, guiding the inflammatory response toward a more balanced state. In acidic environments, which are typical during inflammation, its amino groups

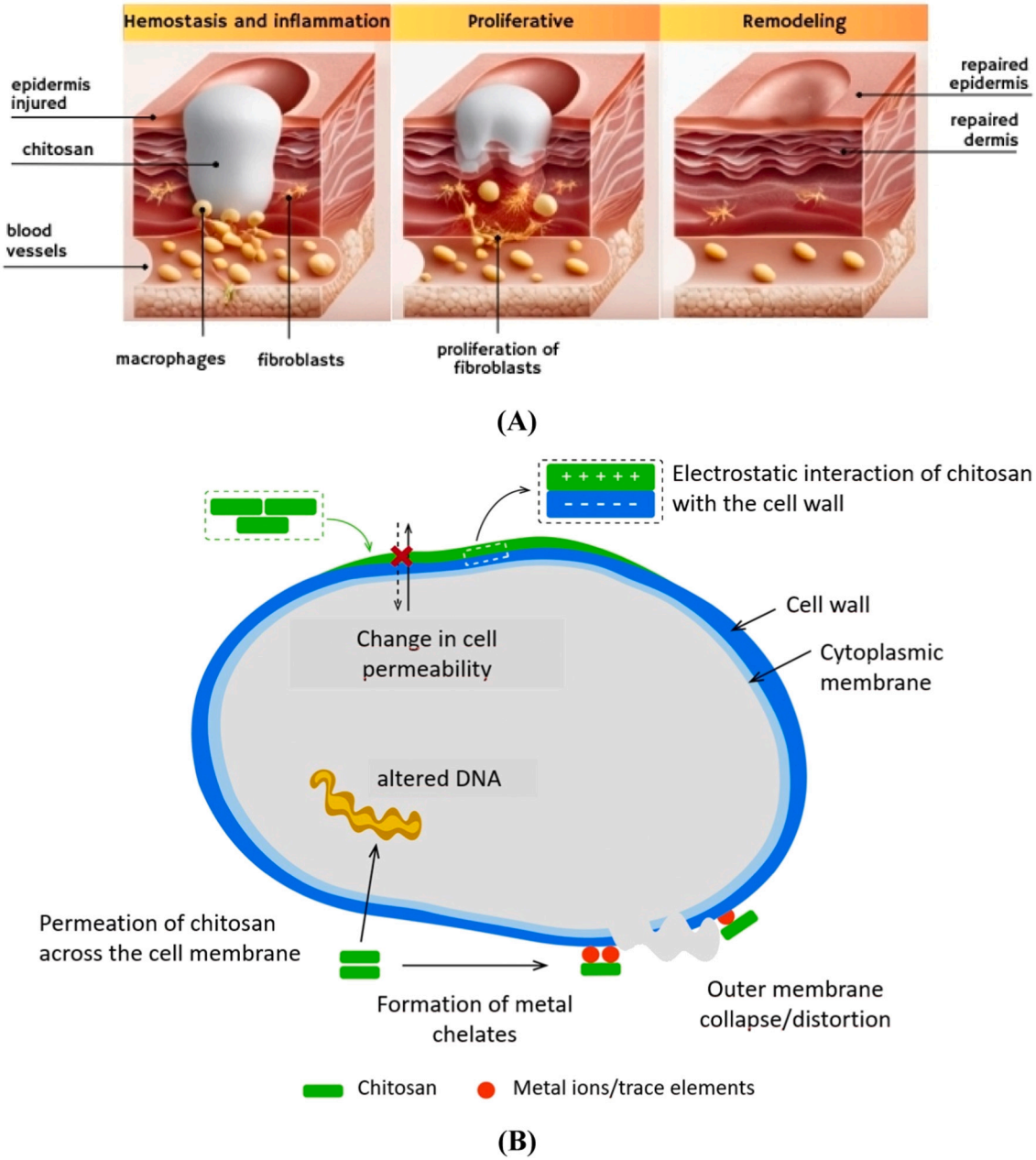

Fig. 2. (A) Schematic representation of wound repair phases and the action of CS in the process. (B) Schematic representation of the main mechanisms of action of chitosan against microorganisms. Adapted and reprinted under Creative Commons Attribution 4.0 (CC BY) license and permission from ref. [17]. Copyright 2022 EditSBQ.

become protonated, potentially neutralizing algogenic substances and indirectly contributing to pain relief and improved control of the inflammatory process. These combined mechanisms position chitosan as a promising therapeutic agent for inflammation modulation [20,25].

Approximately 48 to 72 h after the injury, which coincides with the inflammatory phase, the proliferative phase starts with the arrival of neutrophils, macrophages, epithelial cells, and fibroblasts. Specific growth factors decisive for the formation of granulation tissue (a type of new connective tissue) are then released. They are characterized by the deposition of collagen and other extracellular matrix components, along with the formation of new blood vessels (angiogenesis) that fill the tissue gap [18]. An important effect of CS during the proliferative phase is its ability to form granulation tissue [10]. Studies have shown that CS causes macrophages and fibroblasts to release cytokines and growth factors, particularly transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF). These growth factors trigger the migration of macrophages to the injured areas, stimulating fibroblast proliferation, increasing collagen and glycosaminoglycans secretion, and enhancing the proliferation of endothelial cells. CS can also promote angiogenesis in the developing tissue, serving as an essential structural support for the formation of new blood vessels. Together, these events are crucial for granulation tissue formation [22,24].

The remodeling phase is the final stage of wound healing, where type III collagen produced during the proliferative phase is gradually replaced by type I collagen, making scar tissue stronger and more resilient. The structure of chitosan, which resembles the natural extracellular matrix, facilitates the reorganization of collagen fibers, resulting in a more functional scar [10,18]. Fig. 2A shows a representation of the cited phases of wound repair.

The moist and nutrient-rich environment of skin wounds provides desirable conditions for the growth of pathogenic microorganisms. Bacterial infections are known to occur when the host's immune system fails to eliminate all invading microorganisms. Therefore, the antibacterial properties of dressings need to be seriously considered. As reported by several authors, CS has antimicrobial effects on the inactivation of bacteria, fungi, protozoa, and viruses in different clinical situations, making it widely applied as a bioactive dressing [26–28]. However, its antimicrobial mechanisms are not completely elucidated. The most widely accepted antimicrobial actions are: (i) alteration of membrane or cell wall permeability, leading to rupture; (ii) interaction with microbial DNA, inhibiting mRNA and protein synthesis; (iii) chelation of essential metal ions, hindering microbial growth; and (iv) formation of a polymeric film on the cell surface, blocking gas and nutrient exchange and causing cell death. Additionally, these mechanisms may act simultaneously, enhancing the antimicrobial efficacy of CS [10,17]. Fig. 2B shows a schematic representation of these main mechanisms.

Regarding bacteria, it is known that in Gram-negative bacteria (G-) the inner layer of the membrane is composed exclusively of phospholipids, while the outer layer is comprised of (negatively charged) phospholipids and lipopolysaccharides. Differently, the cell walls of Gram-positive bacteria (G+) are composed of peptidoglycans and teichoic acids. The surface of G+ bacteria is negatively charged due to the presence of carboxyl and phosphate groups of teichoic acids [10]. When CS is dissolved in acidic aqueous solutions, the NH_2 groups are protonated into cations NH_3^+, leading to electrostatic interactions between the protonated group and lipopolysaccharides in the G- cell membrane, or G+ teichoic acids, and consequently resulting in an uneven distribution of negative charges in the bacteria. This process promotes the dissolution of the bacterial cell wall, which is deformed and ruptured under unsustainable osmotic pressure, subsequently causing cellular content leakage, i.e., cell lysis [13,26,29,30]. Xing, K. et al. [28] observed that CS molecules adhered to the surface of *S. aureus* and *E. coli* after 30 min of contact, causing ruptures in the cell walls and cellular content leakage for both bacterial strains. Furthermore, CS can penetrate the bacterial cell wall to form complexes with DNA, which ends up impairing the function of DNA polymerase and RNA polymerase, consequently suppressing DNA and RNA replication and transcription, and inhibiting bacterial proliferation [31]. Nevertheless, due to the different physicochemical characteristics found in CS samples (e.g., molecular weights, acetylation degrees, etc.), it becomes challenging to standardize and choose the ideal CS (in relation to its chemical structure) for disinfecting microorganisms present in skin wounds. Additionally, many studies using CS for this purpose do not clarify its physicochemical characteristics, often generating ambiguous and questionable results and making it difficult to consolidate the application of CS-based biomembranes for wound treatment in clinical practice [32,33].

3. Methods for structuring chitosan-based materials

In the field of tissue engineering and regenerative medicine, the versatility of manipulation of CS allows its use in different forms, each offering unique advantageous applications. This section delves into the methodologies employed to structure CS-based materials, covering a wide range of techniques. These methods not only highlight the adaptability of CS as a biomaterial, but also underscore innovation in engineering approaches aimed at enhancing skin repair and regeneration. Fig. 3 summarizes the main structuring methods used in CS-based materials for tissue repair.

3.1. Thin films

CS-based films, produced by a casting method, serve as semi-permeable dressings that facilitate the exchange of gases and vapors. These films effectively block microorganisms and water droplets, creating an ideal moist environment for wound healing. Their transparency allows wound monitoring in real time, while their elasticity, softness, and self-adhesive properties make them versatile and appropriate for application in various skin areas. However, the creation of thin

Fig. 3. Morphological forms of CS-based materials.

films for use as dressings encounters significant challenges concerning their mechanical properties and limited exudate absorption capacity [1]. To address these issues, the main strategy involves the development of hybrid films (blends) that combine materials to enhance both mechanical properties and exudate absorption, making the dressing more hydrophobic. Thus, the formation of hybrid films seeks to produce dressings with optimized properties for effective wound healing applications [34].

Gonçalves et al. [35] developed an innovative antimicrobial film dressing by incorporating CS, poly(vinyl alcohol) (PVA), ε-Polylysine, and glycerol. This blend resulted in films with optimal mechanical and antibacterial properties, being particularly effective against both G- and G+ bacteria. The improved mechanical properties were achieved by adding glycerol as a plasticizer. The swelling behavior, semi-occlusion, and lack of cytotoxicity of the films suggest that they could be highly effective in wound healing scenarios.

Finally, Pereira et al. [36] produced CS films embedded with Mansoa hirsuta fraction (CMHF), which was considered a significant leap in wound healing technology. These films, prepared by a casting technique, not only showed improved mechanical strength and increased thickness, but also resulted in rapid wound closure, cell growth, and collagen production. According to the authors, Mansoa hirsute fraction (MHF) molecules act as plasticizers, leading to increased mobility of polymer chains, and consequently improving the mechanical strength of the films. This breakthrough evidences the potential of CS films to enhance healing processes and promote tissue regeneration, marking a notable advancement in the field of wound care materials.

3.2. Nanoparticles

The use of CS in nanoparticle (NP) formation for biomedical applications represents a significant advance in nanomedicine due to its unique properties and ability to facilitate targeted drug delivery [37]. The primary challenge in this field is to understand the key supramolecular forces involved in NP formation and stabilization, which are essential for producing nanoparticles with tunable properties. However, significant progress has been made in recent decades with the development of research on the physicochemical properties of CS in both solid and aqueous states, providing a stronger foundation and allowing a more rational nanoparticle production [38]. Moreover, the incorporation of formulations into CS NPs has proven to enhance the therapeutic efficacy of encapsulated drugs, enabling controlled release mechanisms and improving the stability of drug compounds. In this context, CS-based NPs have been extensively explored for various biomedical applications, including cancer therapy, where they can be engineered to target tumor cells specifically, thereby reducing the side effects associated with conventional chemotherapy. These NPs have also been used in gene therapy as vectors for delivering genetic material into cells, evidencing their versatility and potential for the advancement of personalized medicine [37,39].

In their study, Choudhary et al. [40] explored the potential therapeutic effect of quercetin, a dietary flavonoid known for its wide range of health benefits, on wound healing through its encapsulation in CS-based NPs. The research demonstrated that quercetin-loaded NPs, synthesized via ionic gelation, significantly improved wound healing by modulating the expression of critical cytokines and growth factors involved in the wound healing process. The use of NPs promoted a controlled release of quercetin, leading to an optimized anti-inflammatory and pro-healing response. The findings suggested that the application of quercetin NPs improved the healing quality and the granulation tissue maturity, evidenced by increased blood vessel density, reduced inflammatory cell infiltration, enhanced fibroblast activity, and more organized collagen deposition and arrangement. Thus, this study provides a novel insight into the use of quercetin-loaded CS NPs as an effective strategy for cutaneous wound healing, highlighting their potential to improve therapeutic outcomes in wound management through bioactive flavonoid delivery.

CS is also widely recognized for its ability to stabilize NPs, offering a biocompatible and environmentally-friendly solution for various applications, including drug delivery systems, biomedical engineering, and catalysis. Its unique cationic nature and the presence of functional groups, such as amino and hydroxyl groups, allow CS to effectively interact with and stabilize NPs. This interaction prevents the aggregation of NPs, maintaining their dispersibility and stability in various media. Furthermore, the biodegradability and non-toxicity of chitosan make it an ideal stabilizing agent, capable of enhancing the biocompatibility of NPs for medical applications. The ability of CS to form stable complexes with metal ions and the viability of its derivative production further expand its utility in NP stabilization, enabling the targeted delivery of drugs and the development of responsive systems for therapeutic and diagnostic purposes.

The use of CS as a stabilizer agent of gold NPs (AuNPs) and their application in the controlled release of tea tree oil were reported by Matussek et al. [41]. The AuNPs were successfully incorporated into the CS matrix using two different approaches: the formation of NPs within a CS solution in the absence of citrate and the combination of a CS solution with an AuNP solution (with sodium citrate) produced separately. The findings demonstrated that the presence of citrate influenced the stability of the films in water since the film without this agent turned into a gel. On the other hand, the droplets remained intact during the controlled release experiments, regardless of the presence of citrate during the formation of AuNPs. The release time of tea tree oil was about 25 h for both films and droplets, indicating that in addition to CS, AuNPs also interacted with tea tree oil within the polymer matrix, delaying the release process.

A preclinical study evaluated the antibacterial effect of chitosan–propolis nanoparticles (CS NP) against *Enterococcus faecalis* biofilms from patients with failed root canal treatments by comparing nanoparticle formulations (100 and 250 μg/μL) with propolis, chitosan, calcium hydroxide (CH), and 2 % chlorhexidine (CHX). The results demonstrated that CS NPs effectively reduced *E. faecalis*, outperforming bare chitosan and propolis, with efficacy comparable to CH and CHX as intracanal medications [42].

3.3. Electrospun nanofibers

Electrospun nanofibers (NFs) are a cutting-edge class of materials characterized by their ultrafine dimensions, typically in the nanometer scale, which can be obtained through electrospinning. Such technique consists of an electrohydrodynamic process where an electrostatic field moves a fluid, stretching polymer solutions to form fibers with diameters from micrometers to nanometers [43]. The equipment is comprised of a high-voltage power supply, a polymer solution reservoir (syringe), an injection system, and a collector, while the NF formation process includes four steps: (i) electric charge formation in the polymer droplet and Taylor cone creation; (ii) jet stretching along a straight line; (iii) jet thinning in the electric field and increased instability; and (iv) jet solidification and collection as a solid fiber.

As the fibers produced can have different diameters, electrospinning represents an invaluable method for fabricating materials with unique properties, such as high surface area to volume ratio and porosity. The parameters of electrospinning, e.g., solution concentration, applied voltage, flow rate, and ambient conditions, are fundamental to control the properties of the resulting NFs, including their diameter, morphology, and mechanical strength [44]. Such technique allows the fabrication of CS-based NFs that mimic the natural extracellular matrix, promoting cell adhesion, proliferation, and wound healing [45–47].

Electrospun CS NFs have been widely used in the development of advanced wound dressings. These nanofibrous dressings provide a protective barrier against infection while simultaneously supporting the natural healing process. The high porosity and moisture retention of the nanofiber mats ensure a suitable microenvironment for wound healing,

facilitating gas exchange and maintaining optimal moisture levels at the wound site. Moreover, the flexibility and conformability of electrospun dressings allow them to adhere closely to the wound surface, offering comfort to the patient and reducing the risk of secondary infections [36–38]. Nonetheless, there are some challenges associated with electrospun CS nanofibers, for instance, poor fiber formation, limited mechanical strength, and solvent compatibility. Chitosan has low electro spinnability and requires a strong electric field due to its polycationic nature caused by the presence of amino groups on its backbone. Additionally, CS needs specific solvents (such as acidic solutions) to dissolve, which can limit the electrospinning process. These challenges are often overcome by using *co*-spinning with natural or synthetic polymers. Chitosan is commonly used in conjunction with materials like collagen, zein, silk fibroin, polyethylene oxide (PEO), polylactic acid (PLA), PVA, and zein [48].

The integration of CS with other polymers like PEO further enhances its physical and biological properties, making it even more effective in medical applications, as reported by Sharifi et al. [49]. The addition of magnetic NPs such as copper ferrite ($CuFe_2O_4$) to the CS/PEO NFs introduces unique functionalities to the scaffold, for example, improved mechanical properties and magnetic behavior. These magnetic NPs exhibit excellent antibacterial and antioxidant properties that are essential for preventing infections and reducing oxidative stress at wound sites. Specifically, the addition of $CuFe_2O_4$ NPs has shown to improve the wound healing process by promoting fibroblast migration and growth, which are critical steps in tissue repair.

Li et al. [50] investigated the innovative use of *Periplaneta americana* (a type of cockroach) residue for producing electrospun CS NFs aimed at enhancing infected wound healing. By recognizing the environmental impact and resource waste of post-extraction residue disposal of *Periplaneta americana*, this study proposed a sustainable approach by deriving low and high molecular weight CS from these residues. Through electrospinning, these CS were spun into NFs using a blend of polyvinyl alcohol (PVA) and PEO in order to take advantage of their excellent mechanical, antibacterial, and biocompatible properties. The authors meticulously compared the physicochemical properties of the derived CS and its commercial counterparts, revealing the superiority of *Periplaneta americana*-based CS in terms of purity and quality. The electrospun NFs, optimized due to their composition and spinning conditions, exhibited remarkable properties, including enhanced mechanical strength (the CS mechanical properties were improved by PVA and PEO blend formation), excellent antibacterial activity against common pathogens, and promising biocompatibility, as evidenced by in vitro and in vivo evaluations.

3.4. Hydrogel

Hydrogels provide a moist environment conducive to wound healing, effectively absorb exudates, and can be engineered to deliver therapeutic agents directly to the wound site [51]. Different from other structures, hydrogels possess network structures in three dimensions (3D) composed of cross-linked polymer chains, which causes them to absorb substantial amounts of wound exudate. High-performance hydrogels can be synthesized by modifying the active hydroxyl and amino groups present in chitosan (CS), making them ideal for wound healing applications [47]. CS-based hydrogels are formed through various physicochemical interactions and are categorized based on their cross-linking mechanisms into “reversible” or “physical” gels and “permanent” or “chemical” gels. The physical gel process connects chitosan polymer chains through non-chemical interactions, such as ionic, electrostatic, or hydrogen bonding. In contrast, the chemical gel forms a stable three-dimensional structure via covalent bonds, where amino and hydroxyl groups present in the chitosan chain interact with the cross-linking agent. The most common cross-linking methods for chemical gel formation are Schiff base and amidation reactions [48]. Chitosan hydrogels require specific conditions for effective gelation, such as acidic pH and cross-linking agents, which end up limiting their versatility in various applications. Additionally, their low mechanical strength makes them fragile and unsuitable for certain uses without modification or reinforcement [52].

The incorporation of other bioactive components such as growth factors or NPs into hydrogels can further optimize the healing process by enhancing cellular activities essential for tissue repair [53,54]. In this way, the application of CS-based hydrogels in dressings offers a multifaceted approach to wound management [53]. These materials not only serve as protective barriers against infection, but can also actively participate in the healing process by delivering bioactive molecules in a controlled manner [12]. The versatility of CS allows the formulation of stimuli-responsive hydrogels that can be sensitive to environmental wound changes, e.g., pH shifts, ensuring that therapeutic agents are released when most needed [55,56].

A comprehensive study conducted by Che and colleagues [51] emphasized that CS-based hydrogels can be created using various cross-linking methods due to their three-dimensional network that can accommodate many aqueous solvents and biofluids, making them ideal for the encapsulation and protection of drugs. This capability makes CS-based hydrogels excellent materials for skin dressings, as they promote skin repair at different stages of the healing process. Another review published by Guo et al. [57] highlighted the remarkable properties of CS, including the prevention of microorganism dissemination and its positive influence on the aggregation of platelets and red blood cells, contributing to a favorable hemostatic outcome. CS-based hydrogels are known for their bioadhesion, soft texture similar to the extracellular matrix, and ability to carry therapeutic molecules or growth factors, allowing the regulation of drug release and promoting faster and more effective wound healing.

In another study, Thirupathi et al. [58] investigated a thermo- and pH-sensitive CS derivative hydrogel, which had its dimensions changed depending on the pH of the surrounding environment. This type of hydrogel accelerated cell infiltration and proliferation, thereby facilitating healing, in addition to releasing anti-inflammatory drugs in a controlled manner during the initial phases of wound treatment. In short, these studies underscore the potential of CS-based hydrogels as dressings for a wide range of wounds, including burns and surgical, infected and diabetic wounds on account of their ability to provide a moist environment conducive to healing, effectively absorb exudates, and release therapeutic agents in a controlled manner directly at the wound site.

Chitosan-based hydrocolloids have clinically proven to enhance wound healing. A study conducted by Liu et al. reported significant improvement in patients with chronic and hard-to-heal wounds following the use of chitosan hydrocolloids compared to the control group. The assessment was based on factors such as healing efficiency, itching and pain levels, wound area reduction, dressing change frequency, and overall costs over a three-week period [59].

3.5. Nanoemulsion

Nanoemulsions containing CS are recognized for their ability to encapsulate and deliver lipophilic and hydrophilic drugs efficiently. Because of their nano size, these emulsions facilitate the penetration of therapeutic agents into deeper layers of skin, improving the local bioavailability of drugs at the wound site. In this scenario, the positive charges of chitosan better adhere to negatively charged skin and wound tissues, resulting in longer retention times and sustained (controlled) release of encapsulated drugs. These features make CS-based nanoemulsions a potent tool for treating infected wounds, delivering growth factors, and applying antimicrobial agents directly to the injury site.

Despite their advantages, the production of nanoemulsions presents some challenges, such as stability, size control, and chitosan viscosity. CS nanoemulsions are prone to instability, leading to phase separation or aggregation over time. With respect to size control, variations in

formulation or processing can cause a wide distribution of droplet sizes, making control difficult. Lastly, the natural viscosity of CS can hinder the formation of stable, homogeneous nanoemulsions, thus requiring careful optimization of concentration and processing parameters. To overcome such limitations, ongoing research has focused on the improvement of formulation strategies, stabilizing agents, and production techniques [60].

Recent studies on CS containing nanoemulsions have highlighted their potential in wound healing applications. Perteghella et al. [61] explored nanoemulsions of clove oil stabilized with CS oleate, specifically targeting their antioxidant and wound healing activities. The results revealed that CS oleate effectively stabilized clove oil nanoemulsions, keeping their dimensions around 300 nm and the clove oil content above 80 % for up to four months. These nanoemulsions exhibited significant antioxidant properties comparable to α-tocopherol (a type of vitamin E) and accelerated wound closure in a murine burn model. Histological analysis confirmed the antioxidant and anti-inflammatory activities of such nanoemulsions, evidencing their potential as an effective wound healing formulation.

Another study performed by Ansari et al. [62] evaluated the formulation, physicochemical characterization, and wound healing properties of a crisaborole-loaded CS-based nanoemulsion. Crisaborole is a drug used in the treatment of atopic dermatitis. This study developed four formulas of crisaborole-loaded nanoemulsions using lauroglycol 90, Tween-80, and transcutol-HP. The optimized formulation exhibited a vesicle size of 64.5 nm and showed promising wound healing and anti-inflammatory activities, suggesting that crisaborole-loaded CS nanoemulsions can be effectively used to treat skin wounds.

3.6. Sponge

The use of CS-derived sponges in skin injury and wound treatment takes advantage of the unique attributes of the biopolymer, providing a sophisticated solution beyond traditional hemostasis methods. Traditional approaches often fail to treat complex wounds, carrying risks of thrombosis or proving impractical for mobility. CS sponges, however, offer considerable fluid absorption, facilitating the aggregation of blood cells and platelets for rapid hemostasis, in addition to possessing remarkable compression capability, effectively reducing blood loss. Moreover, CS sponges have an adaptable design, allowing the integration of antibacterial and self-healing qualities that not only prevent infections, but also accelerate tissue regeneration. Due to their versatility in adapting to wound sites and ability to accelerate healing and reduce the risk of infection, CS sponges have represented a significant advancement in hemostatic technology, becoming a powerful tool for treating various skin injuries, from minor abrasions to serious burns and wounds [2,63].

Despite being advantageous, CS-based sponges face several production challenges, particularly concerning their mechanical properties and fabrication processes. Indeed, their mechanical strength is often insufficient, complicating the creation of sponges that combine flexibility and durability for targeted applications. Regarding its fabrication, it is difficult to ensure consistent porosity – a critical factor for effective absorption and drug delivery. Factors such as variations in chitosan concentration, structural configurations, solvent systems, and cross-linking agents can significantly influence the functionality and structural integrity of CS-based sponges. In this sense, current research has sought to improve the mechanical strength and stability of these sponges by incorporating reinforcement materials and utilizing chitosan derivatives [63,64].

Research conducted by Mohandas et al. [65] explored the use of CS-hyaluronic acid composite sponges with VEGF-loaded fibrin NPs to enhance angiogenesis in diabetic wounds, where impaired angiogenesis poses a major challenge. These sponges were considered promising for the sustained release of VEGF, encouraging endothelial cell proliferation, facilitating the formation of capillary-like structures, and consequently signaling potential improvement in wound healing. Lu et al. [66] fabricated a CS-gelatin sponge with tannins and platelet-rich plasma that stands out for its thermostability, mechanical strength, efficient water handling, and inhibition of bacterial growth, resulting in rapid wound repair. The mechanical strength of the CS sponge was improved through the formation of a cross link with the gelatin sponge.

Karoichan et al. [67] investigated a CS sponge cross-linked with guanosine diphosphate for the encapsulation of adipose-derived mesenchymal stem cells (ASCs) and osteogenesis differentiation. This innovative scaffold featured rapid gelation and injectability for minimally invasive regenerative applications, with ASCs maintaining their viability and metabolic activity. The co-encapsulation of pyrophosphatase (PPtase – acid anhydride hydrolase that acts on diphosphate bonds) was fundamental to combat mineralization inhibitions, suggesting the osteoinductive capability of this structure for bone tissue engineering. Du et al. [68] detailed a microchannelled alkylated CS sponge (MACS) designed to treat noncompressible hemorrhage and improve wound healing. This hemostatic sponge with interconnected microchannel architecture excelled in fluid handling and rapid shape recovery, besides showing remarkable pro-coagulant, hemostatic and anti-infective activities and supporting tissue integration and vascularization, proving to be a potential material for the treatment of trauma. Table 1 summarizes the main findings in the literature on the topic over the last ten years and the commercial products available.

4. Conclusions and future perspectives

Recent advances have shown that CS-based materials improve all phases of wound healing, promoting hemostasis, inhibiting bacteria proliferation, and acting as antioxidants and modulating cytokines. Their effects are enhanced in different forms: CS-based films/membranes serve as dressings for burns and wounds, with ideal adhesion and porosity; CS-based NPs enable targeted drug delivery, improving drug stability and controlled release; CS-based NFs mimic the extracellular matrix, supporting cell adhesion and healing; CS-based nanoemulsions treat infected wounds by delivering growth factors and antimicrobials; and CS-based sponges offer improved hemostasis. Despite these advantages, their widespread clinical use faces some challenges, including poor solubility, limited mechanical strength, and insufficient exudate absorption. Improvements such as the incorporation of drugs or metallic nanoparticles can expand the functionality of their properties, however, they may introduce some cytotoxicity. Additionally, the variability of CS physicochemical characteristics and the standardization challenges hinder their application. Although numerous in vitro and in vivo studies have demonstrated their potential, clinical cases remain scarce, emphasizing the need for further research in order to optimize CS-based materials for specific medical uses.

To overcome these challenges and unlock the full potential of chitosan-based materials, it is crucial that researchers and industry professionals collaborate to address these limitations. From this perspective, current research on CS-based materials has focused on achieving synergistic functions by integrating CS with other materials so as to develop multifunctional biomaterials. Furthermore, efforts have been devoted to creating smart materials that leverage the responsiveness of CS to pH, temperature, and electrical stimuli. These innovations aim to advance CS-based applications in four key biomedical fields: drug delivery systems (DDSs), bone scaffolds, wound healing, and dentistry.

CRediT authorship contribution statement

Conceição de Maria Aguiar Carvalho: Writing – original draft, Investigation. **Bruno Batista da Silva:** Writing – original draft, Investigation. **Samira Faleiros Silva Brianezi:** Methodology, Investigation, Data curation. **Rafaela Cristina Sanfelice:** Methodology, Investigation. **Debora Terezia Balogh:** Methodology, Investigation. **Lívia Assis:** Writing – original draft, Visualization, Funding acquisition,

Table 1
Summary of various CS-based structures for skin repair applications.

Material	Biomedical properties explored	Wound model	Advantages	Ref.
Cast films				
CS; GLY	Antibacterial Antifungal	In vitro	Antimicrobial action against G- (*E. coli*) and G+ (*S. aureus)* and fungus *(B. cereus*); CS/GLY 30 % (*w*/w) proved to be more effective in fibroblast proliferation	[69]
CS; GLY; TUR	Antimicrobial Anti-inflammatory Antioxidant Hemostatic Mucoadhesive	In vivo	CS/GLY/TUR membranes increased the number of fibroblasts and provided greater control of bleeding and inflammation, better wound contraction and acceleration of collagen deposition	[70]
CS; OPU; diePEG	Antimicrobial Antioxidant Hemostatic	–	CS-based films loaded with OPU extract were suitable for accelerating the repair of skin lesions	[71]
CS; SAL	Anti-inflammatory Antiseptic Antimicrobial Antioxidant	–	Mixture of CS and SAL showed an attractive SAL release profile for biomedical and cosmetic applications	[72]
CS; MHF	Antimicrobial Anti-inflammatory Antifungal Immunomodulatory	In vivo	MHF exhibited the potential for repair and regeneration of skin lesions due to its anti-inflammatory and immunomodulatory activities	[73]
CS; CO	Antimicrobial Anti-inflammatory Antioxidant	–	Addition of CO oil into CS films decreased the material's affinity with water and increased its resistance	[74]
CS; SF; SA; DS	Antimicrobial Biocompatibility	In vitro	SF/CS/SA membranes showed potential for application as dressings, being suitable for controlled release of DS	[75]
CS; GE; IBF	Antibacterial Hemostatic	In vitro	CS/GE films were effective in controlling IBF delivery and exhibited hemostatic and antibacterial actions	[76]
CS; GLY	Antibacterial Antifungal Analgesic Hemostatic	In vivo	CS/GLY films were equivalent to hydrocolloid in terms of epithelialization, edema and ease of removal	[77]
Hydrogel				
CS; PVA	Antifungal Antibacterial Antioxidant Hypocholesterolemic	In vitro	CS hydrogel showed good antimicrobial activity and healing action	[78]
CS; 4-PA; CAT	Antibacterial Hemostatic	In vitro In vivo	CS/4-PA/CAT-1 hydrogel promoted good epithelialization, collagen deposition and fibroblast migration	[79]
CS; GO	Antimicrobial Biodegradability Low immunogenicity	In vitro In vivo	CS-GO showed good biocompatibility, accelerating wound healing and closure rate up to 92.2 % after 21 days	[80]
CS; EXO	Antimicrobial Antioxidant Biocompatibility Biodegradability Hemostatic	In vitro In vivo	EXOs improved the biocompatibility of CS/GLY hydrogel; CS-GLY-EXO hydrogel proved to be viable for replacing full-thickness skin wounds	[81]
CS; RHC	Biocompatibility Biodegradability	In vitro In vivo	RHC-CS showed superior mechanical resistance and lower gelation temperature, favoring cellular infiltration, vessel formation and wound healing	[82]
CS; IP	Antibacterial Antioxidant Biodegradability Hemostatic	In vitro In vivo	CS/IP was efficient for controlled drug release. Hydrogels added with carotenoids shortened wound healing time	[83]
CS; PEG; AgNPs	Antimicrobial Antioxidant	In vitro In vivo	CS-PEG-AgNP showed antimicrobial and biodegradation actions and improved in-vitro antioxidant activity; potential use in diabetic wounds	[84]
CS; PAA; PVP	Antimicrobial	In vitro	CS/PVP showed greater thermal stability than individual CS and PVP, antibacterial activity against *E. coli*, good biocompatibility and drug release profile	[85]
CS; FEN	Anticonvulsant	In vitro In vivo	Hydrogels containing nanocapsules and nanoemulsions allowed better controlled release of FEN and skin adhesion than hydrogels containing unencapsulated phenytoin	[86]
CS; PVA; AS; PLT F68	Antimicrobial Biodegradability Biocompatibility Non-toxicity	In vitro In vivo	CS-PLT F68 showed swelling and gelling properties and rapid and efficient skin wound healing (due to porosity)	[87]
Freeze-drying				
BR; CB-NPs	Analgesic Antifungal Bacteriostatic Biocompatibility	In vitro	Freeze-dried CB-NPs improved the stability of bromelain, enabling its topical use in the form of dry powder or as a raw material for other pharmaceutical forms	[88]

(*continued on next page*)

Table 1 (*continued*)

Material	Biomedical properties explored	Wound model	Advantages	Ref.
	Biodegradability Hemostatic			
CS; cpd.2	Bactericidal Bacteriostatic	–	CS-cpd.2 showed high porosity and wound exudate absorption rate, good moisture absorption, and effective bactericidal and bacteriostatic activities on *S. aureus* under visible light irradiation and in the dark, being viable for PDT and clinical dressing applications	[89]
CS-OA; αTph	Antioxidant	Ex vivo	CS-OA and αTphNE showed proliferative effect on keracinocytes and fibroblasts; αTph was quickly released from the powder, attesting to the feasibility of its daily use on wounds or burns	[90]
CS; HNTs	Biocompatibility	In vitro In vivo	CS/HTNs oligosaccharide allowed better skin re-epithelialization and reorganization than HNTs or CS oligosaccharide separately, proving to be suitable for use in wound healing	[91]
CS; SC; GA	Antibacterial Antioxidant Biodegradability Hemostatic Low cytotoxicity	In vitro In vivo	Chitosan/SC in spray-dried powder and gel promoted wound healing	[92]
Nanoparticles				
PVA; COS; AgNPs	Antibacterial Anti-inflammatory Hemostatic	In vivo	PVA/COS-AgNPs activated the TGFβ1/Smad signaling pathway, accelerating wound healing	[93]
CS-Ag; LPT NPs	Antibacterial Anti-inflammatory	In vivo	CS-Ag-L-NPs loaded sericin hydrogel demonstrated ability to accelerate wound healing and effectively suppress bacterial infections in clinical settings	[94]
CS; HARF; PLGA	Antibacterial Biocompatibility	In vitro	H/CS/PLGA NPs showed non-toxicity over fibroblasts, high antibacterial activity against *S. aureus* and *E. coli*, and enhanced wound closure percentage compared to free HARF and blank NPs	[95]
HEAE-CNPs; ME-CNPs	Antioxidant	In vivo	High β-carotene and zeaxanthin contents promoted controlled release of carotenoids, favoring wound healing and regeneration by decreasing TNF-α and increasing VEGF and collagen skin contents	[96]
CSNPs/VJ/Cz	Antifungal	Ex vivo In vivo	NCs/Vj/Cz showed antifungal effect against *C. albicans* and *A. niger*, stability with significant drug entrapment efficiency, sustained drug release, and complete tissue repair after 7 days of administration	[97]
CS-AgNPs	Antibacterial Antioxidant Low cytotoxicity	In vivo	CS-AgNPs showed enhanced antioxidant activity compared to CS, low cytotoxicity effect, significant improvement in wound healing progression and oxidative stress damage attributed to antibacterial and antioxidant effects	[98]
GA-CSNPs	Anti-inflammatory Antioxidant	In vitro	GA-CSNPs showed enhanced re-epithelialization and significant wound contraction and accelerated fibroblast cell migration, angiogenesis, hexosamine synthesis and collagen deposition	[99]
LMWC-AgNPs	Antibacterial Biocompatibility	In vivo	LMWC-AgNPs showed effective methicillin-resistant *S. aureus* (MRSA) control, enhanced wound healing, reduced toxicity, reduced liver dysfunction, lower body absorption	[100]
NP-CHITARG	Antimicrobial Anticoagulant	In vitro	NP-CHITARG dispersions were found to be non-cytotoxic to fibroblast cells, presented antimicrobial properties and sustained arginine release	[101]
Nanofibers				
NF-BP (Chitosan, PVP, PEO) + GO	Biocompatibility	In vivo	NF-BP promoted enhanced wound closure rate compared to control (sterile gauze sponges)	[102]
CC, PEC	Biocompatibility Hemostatic	In vivo	NF-CC showed rapid blood clotting time and better performance compared to Celox™	[103]
CC-PEO NF; teicoplanin	Antibacterial Cytocompatibility	In vivo	NFs showed enhanced antibacterial activity, sustained local antibiotic release profile and exhibited cytocompatibility and significant wound healing activity	[104]
CNF-B	Low cytotoxicity	In vivo	CNF-B showed enhanced wound healing activity, efficient burn skin healing and low cytotoxicity	[105]
HF-PCL-CS	Antibacterial	In vitro	HF-PCL-CS showed local and controlled (over seven days) delivery of wound healing agents and reduced bacterial colonization, proving to be a protective barrier against bacterial invasion	[106]
ND-CS-PVA-ANE	Anti-inflammatory Hemostatic	In vivo	ND-CS-PVA-ANE favored wound healing by inhibiting inflammatory activity, representing a potential treatment for hard-to-heal wounds caused by diabetes	[107]
Sponges				
CS-HA/NLC4	Antioxidant Anti-inflammatory Biocompatibility Biodegradability Hemostatic	In vivo	CS-HA/NLC4 showed enhanced drug delivery to wound sites, improved tissue quality, scar prevention, potential for wound care application	[108]
CSGT	Antibacterial Low toxicity	In vivo	CSGT promoted quick wound healing and exhibited low toxicity and antibacterial properties, showing potential for various biomedical applications	[66]
CS:HBC	Antibacterial Cytocompatibility	In vivo	CS:HBC exhibited antibacterial effect (>99.99 % reduction) and promoted fibroblast growth and wound healing	[109]

(*continued on next page*)

Table 1 (*continued*)

Material	Biomedical properties explored	Wound model	Advantages	Ref.
3D layered-CS/PVA	Hemostatic	In vivo	3D-CS/PVA presented effective bleeding control, promoted regeneration of dermis and restored differentiated adipocytes, accelerating wound healing and reducing scar formation	[110]
CS-Alst-asiaticoside	Cytocompatibility	In vitro	CS-Alst-asiaticoside showed angiogenic activity, enhanced wound healing and controlled asiaticoside release	[111]
TMC NPs/CS	Antibacterial	In vivo	QACN/CS-CS showed enhanced antibacterial activity, promoted acceleration of wound re-epithelialization and angiogenesis and prevented wound infection (anti-adhesion contaminant properties)	[112]
CS-HBC/DB	Biocompatibility Hemostatic	In vitro	CS-HBC/DB showed effective hemorrhage control, favorable biocompatibility and fast fluid absorbability, accelerating blood coagulation	[113]
CS-iturin-AgNPs	Antibacterial Low toxicity	In vivo	CS-iturin-AgNPs showed enhanced re-epithelialization and collagen formation, increased antibacterial activity and low toxicity to organs	[114]
Commercial products				
Chitosan Gel for Wound Healing /Farmácia Eficácia	Antimicrobial Healing	Hydrogel	–	[115]
MaxioCel® MX1010/Axio Biosolutions Private Ltd.	Antimicrobial Hemostatic Hypoallergenic	Wound Dressing	Exudate management, easy application and removal, scar improvement and healing stimulation	[116]
Chitosan Wound Dressing /Anhui Xiaoshan Hope Medical Devices Co, Ltd.	Anti-inflammatory Antibacterial Antiseptic Hemostatic Non-toxic Analgesic	Wound Dressing	Promotion of tissue growth, reduced scar formation, non-irritating and not easily allergic	[117]
Waterproof Chitosan Hydrogel Dressing /Weifang Hota New Material Technology Co., Ltd.	Hypoallergenic	Hydrogel	Absorbent, breathable, soft, comfortable, non-adherent, sterile, and pain-relief; accelerated epithelialization	[118]
Guangzhou Rainhome Pharm & Tech Co., Ltd.	Antibacterial Healing	Wound Dressing	Sterile, disposable, non-adhesive, natural, moisturizing and breathable; reduced scar formation and wound adhesion prevention	[119]
Chitopack S®/ Eisai Co	–	Sponge	Early formation of granulation tissue, no retroactive scar formation	[120]
Chitoflex® HemCon /HemCon	Anti-bacterial Biocompatible	Wound Dressing	Wound sealing and stabilizing effect and bleeding control	[121]

CS: chitosan; **GLY:** glycerol; **TUR:** turmeric; **OPU:** *Opuntia ficus-indica*; **diePEG:** diepoxy-polyethylene glycol; **PVA:** polyvinyl alcohol; **SAL:** salicin; **MHF:** Mansoa hirsute; **CO:** Copaiba oil; **SF:** silk fibroin; **SA:** sodium alginate; **DS:** diclofenac sodium; **GE:** gelatin; **IBF:** ibuprofen; **CAT:** catechol; **4-PA:** 4-glutenoic acid; **GO:** graphene oxide; **EXO:** isolated exosome; **RHC:** human collagen-peptide; **IP:** isolated protein; **AgNPs:** silver nanoparticles; **PEG:** polyethylene glycol; **PAA:** neutralized poly-acrylic acid; **PVP:** polyvinylpyrrolidone; **FEN:** phenytoin; **PLT F68:** pluronic F68; **BR:** bromelain; **CB:** chitosan-bromelain; **cpd.2:** small molecular compound; **CS-OA:** chitosan oleate; **αTph:** alpha tocopherol; **HNTs:** halloysite nanotubes; **SC:** sildenafil citrate; **GA:** gum arabic; **STPP:** tripolyphosphate; **COS:** chitosan oligosaccharide; **LPT:** lupeol (pentacyclic triterpene); **HARF:** harmala alkaloid-rich fraction; **PLGA:** poly(lactic-*co*-glycolic) acid; **HEAE-CNPs**: ethyl acetate extract and **ME-CNPs:** methanol extract chitosan nanoparticle loaded with *D. salina*; **VJ:** Egyptian Thompson Seedless *Vitis vinifera*; **Cz:** clotrimazole; **GA-CSNPs:** gallic acid-loaded chitosan nanoparticles; **LMWC:** low molecular weight chitosan; **CHITARG:** arginine-conjugated chitosan polymer; **NF:** nanofiber; **PEO:** polyethylene oxide; **CC:** chitosan-casein; **PEC:** polyelectrolyte complex; **CNF-B:** chitosan nanofibers loaded with bromelain; **PCL:** polycaprolactone; **ANE:** anemoside B4, **HA:** hyaluronic acid; **AND:** andrographolide; **CSGT:** chitosan-gelatin sponge; **CS:HBC:** hydroxybutyl chitosan sponge; **CS-Alst:** chitosan–aluminum monostearate; **TMC NPs/CS:** quaternary ammonium chitosan nanoparticles; and **CS-HBC/DB:** hydroxybutyl chitosan and diatom-biosilica.

Conceptualization. **Carla Roberta Tim:** Visualization, Conceptualization. **Adriana Pavinatto:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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